Original Article

Worse Survival in Rectal Cancer Patients with Preoperative Radiotherapy Compared to without Radiotherapy in Same Postoperative Pathologic pN1 Classification

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Key Words
Rectal cancer;
Preoperative radiotherapy;
Pathologic characteristics;
Survival

Purpose. In this study, we compared the rectal cancer patients with and without preoperative radiotherapy, to evaluate the change of pathologic characteristics and prognosis.
Patients and Methods. From 2002 to 2007, the cases of primary rectal cancer and receiving curative resection were selected. Totally, there were 1544 cases including 239 cases preoperative radiotherapy enrolled.
Results. After preoperative radiotherapy, the significant change of pathologic characteristics included more percentage of smaller tumor size, ulcerative morphologic type and poor differentiation histological grade in patients with preoperative RT than those of not (all $p < 0.05$). The recurrent incidence, 3-year disease-free and 5-year cancer-specific survival rates of patients with preoperative radiotherapy vs. no radiotherapy were 60.0 vs. 42.8% ($p = 0.04$), 45.0 vs. 59.7% ($p = 0.04$) and 47.6 vs. 64.3% ($p = 0.056$) in pT4 patients, and were 48.1 vs. 30.7% ($p = 0.01$), 52.8 vs. 72.9% ($p < 0.01$) and 51.8 vs. 75.1% ($p = 0.03$) in pN1 patients, respectively. After curative resection of tumor, the prognosis of pN1 patients with preoperative radiotherapy was worse than those without radiotherapy. There was no difference in survival rate of pN0 and pN2 classification between the patients with and without preoperative RT.
Conclusion. Downstage effect of preoperative RT has beneficial impact on long term survival of patients with rectal cancer, but our findings showed that the worse survival rates of pathologic ypN1 classification of patients with preoperative RT then pathologic pN1 classification without preoperative RT. This may be resulted from change of characteristics of cancer cell behavior or insufficient response to show benefits. Further study is necessary to more precisely select suitable patients for receiving preoperative RT.
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Because of specific anatomy and biology of rectal cancer, local recurrence happens easily than colon cancer after resection of tumor and eventually gives rise to systemic metastases. Careful pathological studies have clearly demonstrated that the major cause of local recurrence is the persistence of tumor foci within

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the mesorectum.[1,2] In the past decades, the development of total mesorectal excision (TME) technique to remove entire mesorectum in cancer of middle and lower rectum effectively decreased the local recurrent rate to 5-10%.[3-5] Parallel to improvements in surgical technique, neoadjuvant radiotherapy (RT) also has been shown to significantly decrease local recurrence rate.[6] Even implementing optimal surgical technique of TME, preoperative radiotherapy followed by TME curative resection still effectively decreased in local recurrences rate compared to that of TME alone, however, preoperative radiotherapy did not show improvement of overall survival.[7] Recent meta-analysis including several relevant randomized studies reported that the addition of chemotherapy to preoperative RT (CCRT) significantly increased the complete response rates (OR 2.52-5.27, $p < 0.001$) and decreased local recurrent rates (OR 0.39-0.72, $p < 0.001$) as compared to those of RT alone although also showed no difference in disease-free and overall survival rates at five years.[8] Otherwise, the superiority of preoperative over postoperative RT also was confirmed according to the results that preoperative RT had the advantages of enhanced effectiveness in well-oxygenated tissue, downstaging of advanced tumor and better treatment compliance.[9,10]

Although preoperative RT has the benefits in local control after curative resection of rectal cancer, its benefits in disease-free and overall survival still lack of strongly supported evidence.[7,11-14] Because the response of tumor by preoperative RT treatment is inconsistent, and the pathologic and biologic characteristics of tumor may be changed after RT. Perhaps these factors changed by RT will be possible to influence the prognosis of rectal cancer. At this retrospective study, we compared the clinicopathologic variables of patients with rectal cancer between the groups of receiving preoperative RT or not, to evaluate the effect of RT on survival according to the postoperative pathologic stage of rectal cancer.

Materials and Methods

Totally, there were 1561 consecutive cases with non-stage IV rectal cancer registered and treated in our hospital from 2002 to 2007. Among these patients, 1544 cases, including 239 cases with preoperative RT and 1305 cases without, who received curative resection of tumor were enrolled in this study. The types of operation were classified into anterior resection (AR including high and low), Abdominoperineal resection (APR), trans-anal resection (including endoscopic trans-rectal resection) and others (including subtotal or total colectomy, Hartmann resection and resection combined other bowel or pelvic organs). According to the pathologic report of resection margin, there were 6 patients with R1 resection (including 1 AR, 2 trans-anal resection and 1 others of no radiotherapy group; 1 AR and 1 APR of radiotherapy group). Other 99.6% of patients were R0 resection. All patients had received regular follow-up examinations, including serial serum CEA measurements every 3 months for at least 3 years (later every 4 to 6 months), abdominal sonography or CT scan, chest X-ray, and colonoscopy every 12 months. However, image surveys of the tumor metastasis were arranged immediately for patients with elevated CEA. The clinicopathological data of all patients were recorded in our computer-based cancer registry. The follow-up period ranged from 2.8 to 111.6 months with a mean of 57.1 months. Tumors were classified according to the AJCC stage system, 6th edition.[15]

The neoadjuvant radiotherapy (RT) included short and long course combined with chemotherapy or not. In the short course RT, 500 cGy x 5 days with total 2500 cGy were applied. In long course combined chemotherapy and radiotherapy (CCRT), 180 cGy fraction x 28 days with a total dose of 5040 cGy. The regimens of concurrent chemotherapy were 5-FU (800 mg/m^2/day) plus leucovorin (50 mg/day) as a continuous infusion for 5 days in the group of short course radiotherapy and for 5 days at first week and repeated at fourth week of radiotherapy in the group of long course radiotherapy.

Statistical analysis was performed using SPSS for Windows (Version. 12.0, SPSS Inc, Chicago, IL). Kaplan-Meier method was used to analyze survival and prognostic factors. Pearson's chi-square test was used to analyze the differences in incidence of tumor

recurrence between groups. All *p*-values were two-sided; *p*-values of less than 0.05 indicated statistical significance.

Results

The distribution of clinicopathologic variables between the patients with and without neoadjuvant radiotherapy was shown in Table 1. As compared to the group of neoadjuvant radiotherapy, the percentage of patients with age under 70, male gender, tumor location below 5 cm level, and operation type of APR was significantly more than those of no preoperative RT ($p < 0.05$, Chi-square test). After preoperative RT, the clinicopathologic characteristics were changed, including more percentage of smaller size, ulcerative type and poor differentiation of tumor ($p < 0.05$, Chi-square test). According to the postoperative pathologic stage, the percentage of pT4 classification is significantly lower in patients with preoperative RT than those of not ($p < 0.05$). However, the distribution

Table 1. Distribution of clinicopathologic characteristics

	Case Number (percentage)	
	No preop. radiotherapy	Preop. radiotherapy
Total	1305	239
Follow-up times (month)		
Range	2.8 to 111.6	3.3 to 110.3
Mean	57.1 ± 25.2	51.3 ± 22.9
Age		
< 70	799 (61.2)	176 (73.6)*
≥ 70	506 (38.8)	63 (26.4)
Sex		
Female	609 (46.7)	81 (33.9)
Male	696 (53.3)	158 (66.1)*
Location		
> 10 cm	342 (26.2)	5 (2.1)
5-10 cm	775 (59.4)	157 (65.7)
< 5 cm	188 (14.4)	77 (32.2)*
Operation type		
Anterior resection	1069 (81.9)	181 (75.7)
APR	113 (8.7)	48 (20.1)*
Transanal resection	71 (5.4)	3 (1.3)*
Others	52 (4.0)	7 (2.9)
CEA elevation		
≤ 5	817 (62.6)	147 (61.5)
> 5	488 (37.4)	92 (38.5)
Tumor diameter		
≤ 3 cm	479 (36.7)	124 (51.9)*
> 3 cm	826 (63.6)	115 (48.1)
Gross type		
Polypoid	370 (28.4)	29 (12.1)
Ulcerative	935 (71.6)	210 (87.9)*
Histology		
Adenocarcinoma	1235 (94.6)	216 (90.4)
Mucinous/signet ring cell	70 (5.4)	23 (9.6)*
Histology grade		
Well	220 (16.9)	17 (7.1)
Moderate	1015 (77.8)	192 (80.9)
Poor	70 (5.4)	30 (12.6)*
Examined LN		
< 12	215 (16.5)	33 (13.8)
≥ 12	1090 (83.5)	206 (86.2)
T classification		
Tis/T0	40 (3.1)	5 (2.1)
T1	132 (10.1)	10 (4.3)
T2	251 (19.2)	49 (20.5)
T3	610 (46.7)	135 (56.5)
T4	272 (20.8)	40 (16.7)*
N classification		
N0	741 (56.8)	142 (59.4)
N1	313 (24.0)	52 (21.8)
N2	251 (19.2)	45 (18.8)
TNM stage		
0	40 (3.1)	5 (2.1)
I	311 (23.8)	54 (22.6)
II	395 (30.3)	83 (34.7)
III	559 (42.8)	97 (40.6)
Postop. adjuvant chemotherapy		
No	908 (69.6)	178 (74.5)
Yes	397 (30.4)	61 (25.5)
Postop. adjuvant radiochemotherapy		
No	1253 (96.0)	239 (100)
Yes	52 (4.0)	0 (0)*
Preop. neoadjuvant radiotherapy		
Long course (CCRT)		80 (33.5)
Short course		159 (66.5)
RT alone		125 (52.3)
CCRT		34 (14.2)

* $p < 0.05$ as compared to the same classification of no preoperative RT.

of pN classification, TNM stage and postoperative adjuvant chemotherapy was no difference between the two groups.

The incidence of tumor recurrence, 3-year disease-free survival and 5-year cancer-specific survival rates according to the postoperative pathologic stage were shown in Table 2. In patients with preoperative RT, there were 5 cases (2.1%) with complete response (T0) after preoperative CCRT treatment and one case suffered from recurrence during follow-up periods. There was no recurrent case in Tis classification of patientswithoutpreoperative RT. In pT4 classification, the recurrent incidence, 3-year disease-free and 5-year cancer-specific survival rateswere 60.0 vs. 42.8% (p = 0.04), 45.0 vs. 59.7% (p = 0.04) and 47.6 vs. 64.3% (p = 0.056) in patients with preoperative radiotherapy vs. no radiotherapy, respectively (Fig. 1). The recurrent incidence was significantly higher and the 3-year disease-free survival was worse in the patients with preoperative RT than those of not. Although the cancer-specific survival also was lower in patients with preoperative RT, but did not achieve the statistical significance (p = 0.056). There was no difference in survival of other pT classification between the two groups. The recurrent incidence, 3-year disease free-survival rates and 5-year cancer-specific survival rates of pN1 classification were 48.1 vs. 30.7% (p = 0.01), 52.8 vs. 72.9% (p < 0.01) and 51.8 vs. 75.1% (p = 0.03) in patients with preoperative radiotherapy vs. no radiotherapy, respectively (Fig. 2). The prognosis of pN1 group patients with preoperative radiotherapy was worse than those without radiotherapy. In contrast to the significantly worse survival rates of pN2 than pN1 classification of patients without preoperative RT, the disease-free and cancer-specific survival rates were no significant difference between the pN1 and pN2 classification of patients with preoperative RT. There was no difference in survival rate of pN0 and pN2

Table 2. Recurrent incidence, disease-free and cancer specific survival in patient with and without preop RT

	Preop. RT: no vs. yes		
	Recurrence incidence (%)	3-year disease-free survival (%)	5-year cancer-specific survival (%)
T classification			
Tis/T0	0.0 vs. 20.0*	100 vs. 80.0*	100 vs. 100
T1	5.3 vs. 0.0	96.9 vs. 100	96.7 vs. 100
T2	10.4 vs. 8.2	90.9 vs. 93.6	91.9 vs. 91.8
T3	30.9 vs. 32.1	73.9 vs. 73.8	77.4 vs. 75.0
T4	42.8 vs. 60.0*	59.7 vs. 45.0*	64.3 vs. 47.6
N classification			
N0	13.0 vs. 15.6	88.8 vs. 89.8	91.8 vs. 87.1
T0-2	5.4 vs. 6.8	95.3 vs. 94.7	95.8 vs. 97.1
T3	19.8 vs. 1.5	83.5 vs. 92.0	91.4 vs. 85.1
T4	19.6 vs. 35.3	81.2 vs. 64.1	84.1 vs. 58.3*
N1	30.7 vs. 48.1*	72.9 vs. 52.8*	75.1 vs. 51.8*
T0-2	10.2 vs. 25.0	94.6 vs. 75.0	94.4 vs. 75.0*
T3	31.1 vs. 44.7	73.0 vs. 56.5	75.7 vs. 60.4
T4	45.9 vs. 70.0	54.9 vs. 30.0	65.2 vs. 38.1
N2	58.2 vs. 55.6	49.1 vs. 50.3	50.4 vs. 61.4
T0-2	61.5 vs. 0	42.7 vs. 100	50.4 vs. 100
T3	54.4 vs. 45.2	54.7 vs. 56.8	53.9 vs. 69.7
T4	63.0 vs. 84.6	42.5 vs. 30.8	48.0 vs. 44.4
TNM stage			
0	0.0 vs. 20.0*	100 vs. 80.0*	100, 100
I	6.1 vs. 5.6	94.6 vs. 96.2	91.9 vs. 91.8
II	19.7 vs. 22.0	82.9 vs. 86.2	88.6 vs. 78.7
III	43.1 vs. 51.5	62.1 vs. 51.6	64.4 vs. 61.0

* p < 0.05 as compared to each other.

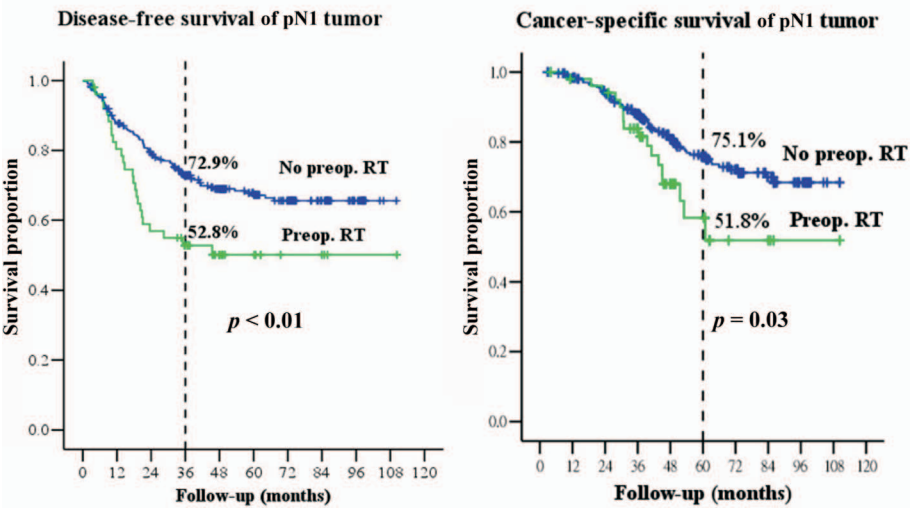

Fig. 1. Disease-free and cancer-specific survival of pN1 tumor.

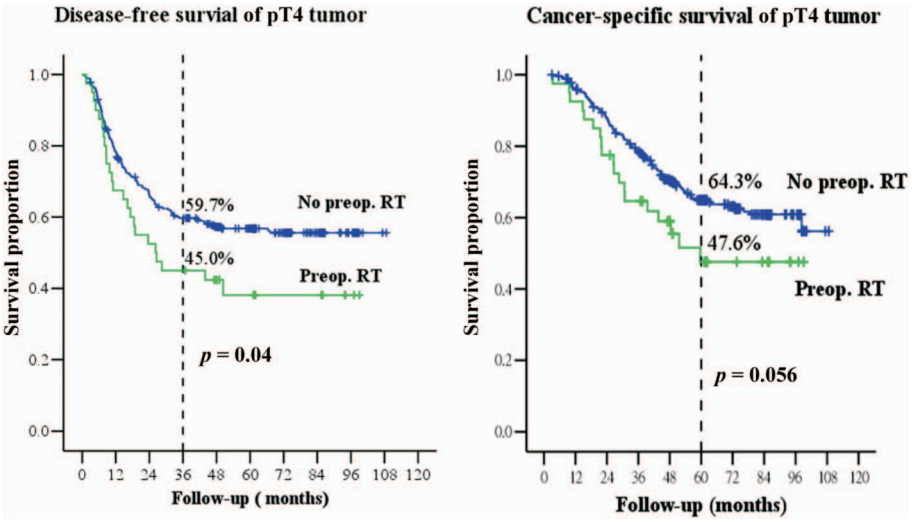

Fig. 2. Disease-free and cancer-specific survival of pT4 tumor.

classification between the patients with and without preoperative RT. There was also no difference in survival of TNM I to III stage between the two groups.

Discussion

In our series, the results revealed that preoperative RT, as compared to no RT group, had different cliniopathlogic characteristics which showed more percentage of small tumor size, ulcerative gross morphology and poor differentiated histological grade. Although the bias of patient selection is possible existence between the two groups, shrinkage of tumor size and residual radio-resistant tumor cells caused by RT effect also has the possibility to change the tumor size, gross type and differentiation of tumor. Complete response rate was 2.1 percent (5 cases) in patients received preoperative RT but still had one case suffered from tumor recurrence. The lower complete response rate of our series may be caused by some patients received preoperative RT alone. Previous meta-analysis had reported that pathologic complete response (ie, ypT0N0) of the resected specimen was observed in 129 of 1096 patients (11.8%) in the CCRT group and in 39 of 1105 patients (3.5%) in the RT group. This difference was

statistically significance (OR 3.65, 95% CI 2.52-5.27, $p < 0.001$).[23] Although bias of patient selection for preoperative RT or CCRT is existent, there was no difference in N classification distribution between the groups with and without preoperative RT. Interestingly, we found that the patients received preoperative RT had higher recurrent incidence and lower survival rates in ypN1 classification as compared to same pN1 patients without preoperative RT. In pT4 classification patients also had similar results. These findings let us doubt that the effect of preoperative RT, if not sufficient, may not provide sufficient benefits for all patients. After preoperative RT, if the postoperative pathologic stage still show advanced T stage or presence of N stage, this may means that only partial or no response of primary tumor to preoperative RT subsequently results into more percentage of radio-resistant tumor cells survived in primary tumor or lymph nodes. Such consequence will cause more aggressive behavior of tumor advances or not still remained unclear. It had been reported that downsize and downstage effect by RT had the benefits on patient prognosis, however, tumor recurrence developed in patients with persistent lymph node metastasis after preoperative RT.[22] Our results also showed that the survival rates of pN1 and pN2 classification was similar in patients received RT and the survival rates of pN0 and pN2 classification were similar between the groups with RT or not. This reflects the possibility that some part of patients with postoperative pathologic pN1 classification actually is cN2 status preoperatively. Down stage effect from cN2 to pN1 by RT may be insufficient to improve survival. According to our findings that there was no difference in survival of pN0 classification between the patients with or without preoperative RT, downstage to pN0 may be necessary to show survival improvement.

How should we assess the response to radiotherapy and its relation to survival benefits? The response to radiotherapy was assessed by a rectal radiotherapy grading system adapted from Mandard et al.[16] This comprised the following: TRG 1: complete response with absence of residual cancer and fibrosis extending through the wall, TRG 2: presence of residual tumor cells scattered through the fibrosis, TRG 3: increase in the number of residual cancer cells with fibrosis predominant, TRG 4: residual cancer out growing fibrosis, TRG 5: absence of regressive changes. According to this system, a recent study reported that the Mandard score combined into TRG1, TRG2 and TRG3-5 was clearly related to both disease-free ($p < 0.001$) and overall survival ($p = 0.012$). On multivariate analysis perineural invasion, nodal status, TRG and circumferential resection margin status were the most powerful predictors of disease-free survival. In contrast T stage and vascular invasion were not found to be independently prognostic on multivariate analysis. When the data were analysed to take into account of node positivity and Mandard score it became clear that in TRG groups 2, 3-5 nodal status plays an important part in future prognosis ($p < 0.0001$).[17] In this study, the results also showed that the local recurrence rate per Mandard score was: TRG1 5%, TRG2 6%, TRG3-5 15% which was not statistically significanton Chi-square testing ($p = 0.24$). The nodal metastasis rate per Mandard score was: TRG1 0%, TRG2 28%, TRG 3-5 50%, this was statistically significant on Chi-square testing ($p < 0.0001$). In comparison the nodal metastasis rate was 0% for ypT0, 0% for ypT1, 17% for ypT2, 49% for ypT3 and 50% for ypT4 ($p < 0.0001$).[17] There was no doubt that patients with pathologic complete response (defined as yT0N0M0) by preoperative CCRT has better long term outcome than those with partial or no response based on recent pooled analysis including 3015 cases.[18] Nevertheless, local recurrence still occurred in 12 cases among the 455 patients with complete pathologic response by CCRT in this pooled analysis. According to these data, we know there was no significant survival benefit if node metastasis still existent after preoperative radiotherapy.

Although the preoperative neoadjuvant radiotherapy had been proved to have better local control of rectal cancer after curative resection, we can not neglect the disadvantage of radiotherapy including higher rates of anorectal dysfunction, side effect of radiation and morbidity has negative impact on quality of life and worse social function of patients.[19,20] In patients with pathologically staged T3, N0, M0 tumors of the upper rectum who have undergone TME with 12 or more nodes removed, the addition of chemora-

diation has very little benefit.[21] So, how to select suitable cases with rectal cancer to receive preoperative RT or CCRT need further study to make sure the survival benefit of patients.

In conclusion, downstage effect of preoperative RT has beneficial impact on long term survival of patients with rectal cancer, but our findings showed that the worse survival rates of pathologic ypN1 classification of patients with preoperative RT than pathologic pN1 classification without preoperative RT. This may be resulted from change of characteristics of cancer cell behavior or insufficient response to show benefits. Further study is necessary to more precisely select suitable patients for receiving preoperative RT.

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原　著

在術後病理同為 pN1 分類之直腸癌患者中，接受術前放射線治療者比未接受族群，其生存期明顯較差

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目的　本篇文章比較直腸癌術前接受和不接受放射線治療的兩組病患，分析評估其病理特徵及預後變化。

方法　挑選 2002 年到 2007 年間原發直腸癌接受根治性切除的新發病例。共 1544 個病患，其中包括 239 個病患術前接受放療。

結果　病理特徵變化方面，術前有接受放療比沒接受放療之患者其小體積腫瘤、潰瘍形態和分化不良之腫瘤比率較高 (均 $p < 0.05$)。患者術前有接受與無接受放療比較，其復發率、3 年無病率及 5 年癌症特異生存率，在 pT4 之腫瘤分別為 60.0 與 42.8% ($p = 0.04$)，45.0 與 59.7% ($p = 0.04$) 和 47.6 與 64.3% ($p = 0.056$)；在 pN1 之腫瘤，分別為 48.1 與 30.7% ($p = 0.01$)，52.8 與 72.9% ($p < 0.01$) 和 51.8 與 75.1% ($p = 0.03$)。術後病理為 pN1 之直腸癌患者，術前接受放療比無放療的群組生存期明顯較差。放療與否在 pN0 和 pN2 組的預後則無差異性。術前未接受放療的病患，pN2 明顯比 pN1 存活率較差，但在術前接受放療的病患，無病率和癌症特異性生存率在 ypN1 和 ypN2 之間則沒有顯著差異。

結論　術前放射治療直腸癌病患的腫瘤分期降階使長期生存有好的影響。但我們的研究顯示，術前放療若最終病理報告為 ypN1，則病人比未放療之 pN1 有較差的存活率，這可能導因癌細胞特性的改變或放療反應不足無法顯示出改善存活率之益處。有必要進一步的研究來更精確地選擇合適的病人接受術前放療。

關鍵詞　直腸惡性腫瘤、術前放射治療、病裡特徵、存活率。